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Basic Physical Mechanisms in Radiobiology

J. S. Robertson

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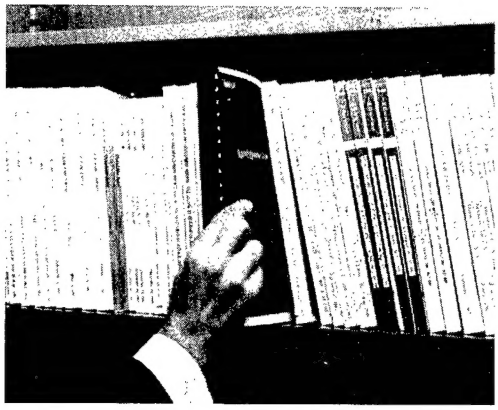

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Basic Physical Mechanisms in Radiobiology*

J. S. Robertson
Brookhaven National Laboratory

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1. Introduction

One of the principal objectives of this symposium is to relate the radiation dose to the biological effects that ensue as consequences. In so doing we begin with the assumptions that ultimately the biological effects are caused, at least stochastically if not deterministically, by the initial physical events that are associated with exposure to ionizing radiation, and that these initial events are followed by a chain of chemical and biochemical reactions that translate the physical events into the biological effects.

Of the physical parameters, the absorbed dose, expressed in terms of energy absorbed per gram at the point of interest, is of prime importance. Experience, however, indicates that the radiation dose per se does not determine the biological effects. Instead, many factors must be considered. These include other physical parameters such as dose rate and ion track density, and many biological factors such as species, age, sex and end point. In particular, for the same end point it has been found that the dose required to produce a given degree of effect depends upon the nature, or type of radiation. The ratio of the dose of a standard radiation, usually 250 kvp X rays or ^{60}Co gamma rays, to the dose of the test radiation required to produce a given effect has been defined as the RBE, or relative biological effectiveness of the test radiation, as mentioned by Dr. Bond in the preceding paper.

In health physics work it is often necessary to accept the existence of RBE's as an empirical fact, and arbitrary or "legislated" values dependent on the LET, or linear energy transfer rate, are used. The values assigned, however, may be based on exposure conditions in which

many of the variables, particularly the dose, the dose rate and the end point, are quite different from those involved in the situation being evaluated, and may not be directly applicable.

One of the problems in radiobiology is to seek a theoretical explanation of RBE's. To insure general validity, this requires determining the RBE's for a wide variety of exposure conditions and end points. We may epitomize the problem by asking, "Why aren't all RBE's equal to unity?"

In the present paper we shall review the basic physicochemical mechanisms involved in the interaction between ionizing radiation and the absorbing material, but may as well admit at the beginning that at present there is no completely satisfactory answer to the above question. In part this is because that while much is known about the effects at each of several stages - physical, physicochemical, chemical, biological, clinical - the mechanisms of transition between the stages is often not well understood.

2. Physical Phase

Ionization and excitation

In the passage of ionizing radiations through any absorbing medium, the primary processes that occur are ionization or ion pair production and excitation, which are distinguished by whether an electron is removed from an atom or merely elevated to an abnormally high energy state. In ion pair production there is removal of an electron from one atom and electron attachment to another. The ionization potential varies with the material, and is about 16 ev air, 13 ev for water. However, on the average, about 32.5 ev are dissipated per ion pair, so for each ion

pair there is another 10-20 ev to be accounted for and which is dissipated by excitation. The excitation energy is disposed of by dissociation, fluorescence or energy transfer. In complex molecules it may appear as vibrational or oscillatory energy. Although direct measurements in water are difficult to achieve, it is inferred from other results that in aqueous media the energy is roughly equally divided between excitation and ionization. The relative importance of excitation in producing biological effects is not known.

Although, at least in such devices as roentgen meters, only the ionization is actually measured, dosimetric values are usually expressed in terms of the total energy absorbed.

Ionization tracks may be studied in cloud chambers, bubble chambers and emulsions. The separation of ion clusters depends on the nature of the radiation, with gamma rays producing relatively sparse tracks having only about 10 ion pairs/μ of path length, whereas alpha particles may have, typically, about 5000 ion pairs/μ, and uranium fission fragments over 100,000 ion pairs/μ. In terms of LET, the values run 0.28 keV/μ for 20 MeV γ rays, 2.8 keV/μ for 200 kvp X rays, 150 keV/μ for 5.14 MeV α particles and 4000 keV/μ for uranium fission products. Highly accelerated heavy charged particles, however, have low LET values. A more detailed consideration of specific types of radiation follows.

Heavy charged particle

In their passage through absorbing material, the heavy charged particles transfer their kinetic energy to the medium mostly by inelastic collision reactions with electrons. This process is described by the Bethe formula:

$$-\frac{dE}{dx} = \frac{4\pi z^2 e^4}{mv^2} NZ \ln \frac{2mv^2}{I}$$

where: $-\frac{dE}{dx}$ = rate of loss of energy by primary particle

e = charge of electron (4.8025×10^{-10} abs esu)

ze = charge of particle (z an integer)

v = velocity of particle

m = mass of electron (9.1091×10^{-28} gm)

Z = electrons/molecule in medium

N = density of molecules in medium

I = mean excitation potential

The above formula is a simplification of the more complete form, which includes additional ter for corrections for very low and for very high velocities. Since v velocity appears in the denominator, $-\frac{dE}{dx}$ becomes smaller for high ocities, which in turn means high energies. In the GeV energy range, protons and other accelerated particles have $\frac{dE}{dx}$ values that may be as low as those for gamma rays. Minimal $\frac{dE}{dx}$ values are about 0.22 keV/μ.

Protons with energies of 0.5 to 1.5 MeV have short, thick, straight paths, with $\frac{dE}{dx}$ values typically 30 to 40 keV/μ in water. This rate of energy loss produces about 1000 ion pairs/μ in ater. Alpha particles of the same or somewhat higher energy typically have $\frac{dE}{dx}$ values of 150 keV/μ and produce 5000 ion pairs/μ in water. As may be seen from the stopping formula, the most intense ionization is produced near the end of the particle's range, where the velocity is low. Near the end of the track a maximum value is reached, after which the $\frac{dE}{dx}$ falls rapidly to zero as the particle comes to rest. This peak is known as the Bragg peak.

Some examples of particle energies that may be encountered are:

Radioactive nuclides	5-6 MeV alpha particles
BNL AGS	33 GeV protons
Proposed Weston AGS	200 GeV
Berkeley Omnitron	1.4 GeV protons 70 GeV uranium nucleus

The above energies are, of course, those of the primary particles in the main beam. Since direct exposure of personnel to the beam is not ordinarily permitted, consideration of the biologic effects of such exposures is of more radiobiological than of health physics interest. In practice, a more frequent source of radiation hazard is the secondary radiation that arises from the reactions of the main beam with shielding and other materials in its path.

In a cloud chamber α-particle tracks may be seen to include short, faint straggling tracks branching from the main track. These are due to recoil electrons and are known as delta rays. The recoil electrons can receive a maximum energy corresponding to twice the α-particle velocity:

$$E_{MAX} = 2mv^2$$

For a 10-MeV α-particle, the most energetic delta ray will have an energy of about 6.3 keV.

Thus not only does the $\frac{dE}{dx}$ for a given type of radiation vary along the track length as a function of the residual energy, but there is a spectrum of LET values within any small segment of the track. This aspect of the problem is discussed more extensively in other papers at this symposium, as is the relationship between LET and $\frac{dE}{dx}$.

3. Electrons, Positrons and Mesons

The absorption of the energy of the lighter charged particles involves essentially the same mechanisms as have been described for the heavy particles. However, because of their lower masses, the velocities for electrons and positrons are much higher for given energies, and the necessity for relativistic velocity corrections arises at lower energies. Positrons and π^- mesons have the additional feature of energy-releasing reactions at the ends of their tracks. Positrons react with electrons to produce two 0.511 MeV gamma rays which are emitted in opposite directions. The π^- mesons react with atomic nuclei to disrupt them and produce "Stars," or multiple tracks associated with the nuclear fragments.

The deceleration of high speed electrons, particularly in dense target materials, results in another kind of radiative emission called bremsstrahlung, or braking radiation. This is a continuous spectrum of X rays, the characteristics of which depend on the electron energy and on the composition of the absorbing medium. For electron energies above 50 MeV, this mechanism becomes competitive with inelastic collision as a mechanism of energy loss, but at lower energies it is of minor importance in radiobiology.

4. Electromagnetic Radiations

Electromagnetic radiations are generally present as a "contaminant" of other kinds of beams and are produced by many reactions of accelerated particles with shielding materials. They are characterized by their wavelength, which is related to their energy:

$$\lambda = \frac{c}{\nu} \quad \text{cm}$$

$$E = h\nu = \frac{hc}{\lambda} \quad \text{ergs}$$

$$E = \frac{0.12354}{\lambda'} \quad \text{MeV}$$

where: λ = wavelength (cm)

λ' = wavelength in Angstrom units, A^o

c = velocity of light (cm/sec)

E = energy

h = Plank's constant, 6.6256×10^{-27} erg sec.

It is important to note that as the energy increases, the wavelength decreases. As a rough rule, the wavelength determines the size of the object with which an electromagnetic wave will interact. Thus radio waves, with λ's in cm to many meters (1.2×10^{-16} to 0.025 eV) react with antennas, whereas infrared rays (0.025 to 1.75 eV) react with molecules, and in the visible region (1.75 to 3.55 eV) is found the beginning of excitation in atoms. The photoelectric effect, in which the incident photon disappears and an electron is removed from an atom, begins in the ultraviolet region (3.55 to 90 eV). In the X- and γ ray regions of 0.5 to 5 MeV, Compton scattering becomes the predominant energy absorbing mechanism. In this process the energy of the incident photon is divided between that of a recoil photon of lower energy and a recoil electron. With λ = incident photon, λ' = recoil photon, φ = scattering angle, m_o = electron rest mass, and e = electron charge, the change in wavelength is given by the formulas:

$$(\lambda' - \lambda) = \frac{h}{m_o e}(1 - \cos\varphi) = 0.0242\,(1 - \cos\varphi)$$

where the final numerical value is for $(\lambda' - \lambda)$ in A^o.

Figure 1 shows the Compton scattering photo energy patterns for 500 keV, 1 MeV and 10 MeV incident photons. It can be shown that for the directly backscattered photons ($\varphi = 180^{o}$) the limiting energy is $\frac{m_o}{2} = 0.255$ MeV, where m_o is the electron rest mass.

At gamma ray energies above 1.022 MeV, pair production becomes possible. In this process 1.022 MeV of energy is transformed into a β^-, β^+ pair, and the remaining energy appears as kinetic energy of the particles.

For low Z materials nuclear reactions, (γ,p), $\gamma,n)$, and $\gamma,\alpha)$, occur at garme ray energies above 10-15 MeV.

Figure 2 shows the total absorption, μ, and the true absorption, μ_a, curves in water for photons in the 0.01 to 100 MeV energy range, and the contributions due to scatter σ_a, the photoelectric effect τ, Compton scattering σ_a and pair production, k, components of the curves. Since the density, ρ, of water is 1, the ordinate values may also be given units of cm^{-1}, or fractional linear absorption. The values for water are approximately correct for soft tissues.

Neutrons

Because of their lack of charge and much greater mass, neutrons do not react appreciably with electrons. Their absorption in matter thus involves nuclear reactions only. There are three main processes:

1. Inelastic scattering
2. Elastic scattering
3. Neutron capture

Neutrons may be classified according to their energy:

Slow (including thermal)	0 - 0.1 keV
Epithermal	.1 keV - 0.02 MeV
Fast	0.02 - 10 MeV
High energy	> 10 MeV

Inelastic scattering occurs only for neutrons of several keV or more and leaves the nucleus in an excited state.

Elastic scattering is the only process effective in reducing neutrons to thermal energies. With fast neutrons below 20 MeV and in tissue, where hydrogen is the most important constituent, elastic scattering accounts for 85-95% of the energy transfer. The energy transferred in a collision is:

$$\Delta E = \frac{4m}{(m+1)^2} E \cos^2 \theta$$

where m = neutron energy

θ = recoil angle

After n collisions the neutron energy is:

$$T_{n1} = T_o e^{-n\xi}$$

where T_o = initial kinetic energy of neutron

T_{n1} = median energy of degraded spectrum

$$\xi = \frac{(A-1)^2}{2A} \ln \frac{A+1}{A-1}$$

where A is the atomic weight of the scattering medium

At energies exceeding 20 MeV, neutrons have sufficient energy to disintegrate nuclei on collision, leading to spallation or star formation.

Below 20 keV, in the epithermal region, the most important mode of energy transfer is by elastic collision. Here the recoiling nuclei do not ionize, but initiate atomic and molecular excitations. Neutron capture by nitrogen and hydrogen does lead to ionization, but at energies above 100 eV the cross sections are low. Both of these processes follow the $1/v$ law, so at lower energies the probability of capture increases with $1/\sqrt{E}$. Neutrons are usually slowed to thermal energies before being captured. Table I lists data pertinent to neutron capture in normal tissue.

TABLE I

Neutron Capture in Normal Tissues

Element and isotope	Element fraction in tissue, %	Isotope abundance %	Reaction cross section barns	Energy MeV
O 17	65.	.037	(n,α) 0.4	1.6
H 1	10.	99.98	(n,γ) 0.352	2.2255
N 14	3.	99.6	(n,p) 1.75	.660
Cl 35	0.15	75.5	(n,γ)30.	8.58

Factors affecting dose-effect relationships

The above considerations indicate the principal mechanisms by which the energy of various kinds of radiation is absorbed in matter, and the reasons for there being differences in track density. To a large extent RBE's are associated with these differences, with the denser tracks in general giving the higher RBE's. It is still not entirely clear, however, why the same amount of energy absorbed in a dense track is more effective than in a sparse track.

The explanation appears to lie at the physicochemical level, and involves a complicated interation of many factors. Among these are free radical diffusion rates, the oxygen effect, target theory, and the sensitivity of the irradiated system.

Free radical diffusion rates and the oxygen effect are most important with indirect effects, those which depend on the energy being initially absorbed by solvent atoms rather than directly by target molecules. In the denser tracks the irradiation products of water, the free radicals H and OH, have a higher probability of reacting with each other and forming oxidative radicals such as H_2O_2, rather than diffusing and reacting with solutes which may act as protective agents. The presence of oxygen in solution increases the production of oxidative radicals by radiations having relatively sparse tracks, but has little or no effect in association with the denser tracks.

The survival curves for cells, bacteria, etc. irradiated with high LET-type radiations are typically exponential, whereas those for low LET radiations often have a shoulder before becoming exponential. This phenomenon is usually interpreted in terms of various forms of the hit theory, with either multiple hits being required to affect a single

target or multiple targets having to be hit to produce the observed effect. Evidently if the required number of hits are too widely separated in time, recovery from the first hits is possible and the later hits are less effective. Thus the denser tracks may be more effective in part because the required number of hits are closer together in time. Very large doses are required for the tracks of low LET radiations to be close enough together in space and time to simulate high LET tracks. Studies with low LET radiations show that the effects of high LET radiation begin to be simulated at dose rates of over 10^8 rad/sec. Even this is somewhat lower than had been expected by theory, indicating that some of the free radicals have longer lives than had been expected. More recent data with electron spin resonance methods support the concept of longer-lived radicals.

In summary, it appears that an explanation of RBE in physical and physicochemical terms is going to be possible, but considerably more data on track structure, free radical production, dose rate effects and other related parameters are needed. Several of the other papers presented at this symposium are concerned with recent data and theories in this area.

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Figure Captions

Fig. No.		Neg. No.
1.	Compton scatter energy distribution patterns for 500 keV, 1 MeV and 10 MeV gamma rays.	11-1292-66
2.	Mass absorption coefficients in water for photon energies 0.01 to 100 MeV. The true absorption curve differs from the total absorption curve in not including the elastic scattering component, σ_s. From Hine and Brownell, Radiation Dosimetry.	12-13-65

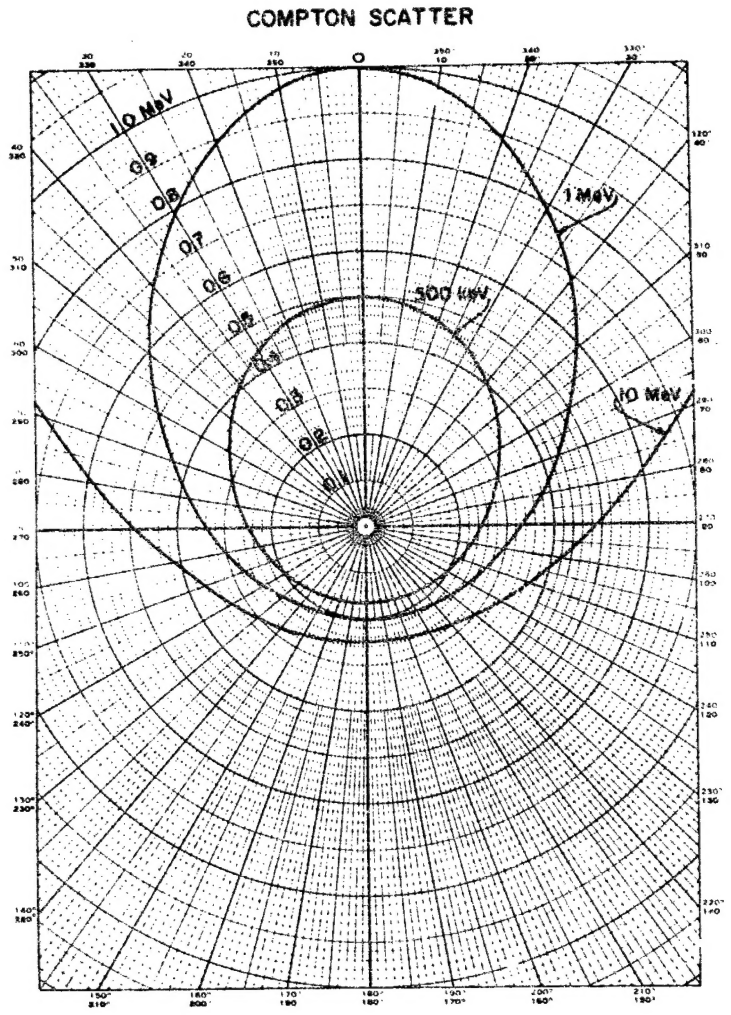

FIGURE 1

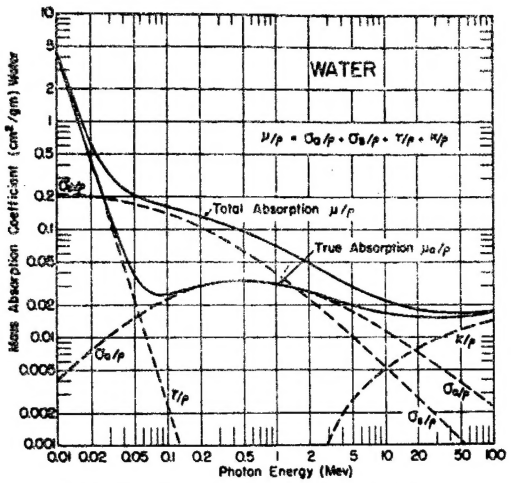

FIG. 17. Mass absorption coefficients for water as a function of photon energy (67).

From: Hine and Brownell
Radiation Dosimetry

FIGURE 2